Claim 2, line 2, delete "general";

line 4, insert --, and-- after the structural formula;

line 5, delete "[" before "wherein";

line 5, delete "]" after "atom";

line 5, insert --,-- after "atom";

line 8, delete "[" before "wherein"; and

line 9, delete "]" after "group".

REMARKS

Claims 1 and 2 are all the pending claims before the Examiner for consideration. Claims 1 and 2 are amended in response to the objections raised by the Examiner as discussed below, and therefore do not raise an issue of new matter.

I. Response to Rejection of Claim 1 under 35 U.S.C. § 103(a)

Claim 1 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Miyamoto et al. (U.S. Patent 5,877,168).

The Examiner states that Miyamoto discloses vitamin D derivatives with substituents at the 2b-position where R_1 represents hydrogen or a hydroxy group and R_2 represents a straight chain or branched lower alkyl group having 1-7 carbon atoms.

Claim 1 is drawn to the 20S-form of vitamin D derivative, whereas Miyamoto discloses the 20-R form. However, the Examiner alleges that one skilled in the art would have been motivated to prepare additional derivatives of vitamin D by modification in the structure taught by Miyamoto.

Additionally, the Examiner states that the compounds of Miyamoto have in vitro calcium regulatory activity and differentiation stimulating activity on tumor cells, and could be used in methods of treatment for diseases caused by abnormal calcium, such as osteoporosis and osteomalacia, or as an antitumor agents.

The Examiner concludes that it would have been obvious to substitute the isomer of Miyamoto since the compounds are structurally similar, and based on their structural relatedness, one would expect them to share common properties.

Applicants traverse for the following reasons.

Contrary to the Examiner's statement, the synthesis of the claimed 20S-forms of the vitamin D derivatives is both complicated and outside the skill of the ordinary artisan. The claimed derivatives are not *prima facia* obvious in view of Miyamoto since Miyamoto does not provide the motivation to prepare such compounds. Furthermore, it would have been difficult for one of ordinary skill in the art to prepare the claimed compounds taking the disclosure of Miyamoto solely into account; Miyamoto does not describe much less suggest a process for preparing pure 20S-forms of these derivatives. Accordingly, the Miyamoto reference does not raise a *prima facia* issue of obviousness for the claimed vitamin D derivatives.

The unexpected biological properties of the claimed 20S forms compared to the 20R forms is additional evidence that the inventive compounds are nonobvious in view of Miyamoto.

In Example 9 of the specification (pages 38-39), the binding affinities of the inventive 20S compounds for bovine thymus 1 α, 25-dihydroxyvitamin D3 receptor (VDR) is shown to be 3 to 12 times higher than the affinities of the 20R forms for the same receptor substrate. Specifically, in the table on page 39, data in the left column are for the comparative 20R-forms while the right column contains data for the inventive 20S forms. A comparison of compound

(4) with compound (72); compound (65) with compound (68), compound (6) with compound (74) and compound (3) with compound (7) reveals this substantial difference in the binding affinities.

Applicants further wish to emphasize the unexpected and improved results obtained for the instant 20S derivatives as provided in Example 10 of the specification and resubmitted as Inventive Example 1 in the unexecuted Declaration under 37 C.F.R. § 1.132 of Mr. Seiichi Ishizuka (an executed version of the declaration is forthcoming and will be filed in due course). For purposes of direct comparison, Applicants have drafted the Declaration to include the experimental data for the 20S derivatives from original Example 10 along with new comparative data for the 20R forms (Comparative Example 1).

In a colorimetric cell assay which measures the ability of the compounds to induce differentiation of the HL-60 cell line vis-à-vis the reduction of nitroblue tetrazolium, the instant 20S-forms show excellent efficacy compared to the 20R-forms. To fully appreciate this difference, comparison of compound (4) with compound (72); compound (65) with compound (68); compound (6) with compound (74) and compound (3) with compound (71) reveals that the 20S-forms are substantially more potent, i.e., require logarithmically lower concentrations, in their ability to induce cell differentiation.

In view of the foregoing arguments, the experimental evidence of record, and the new Declaration evidence, Applicants submit that the rejection of Claim 1 is obviated and request reconsideration and withdrawal thereof.

II. Response to Rejection of Claim 2 under 35 U.S.C. § 103(a)

Claim 2 is rejected under 35 U.S.C. § 103(a) as being obvious over Trost et al. (J.Am.Chem.Soc. Vol. 114, pages 9836-45, 1992).

According to the Examiner, Trost discloses a palladium-catalyzed alkylative cyclization of enynes for the synthesis of vitamin D derivatives.

Whereas according to the Examiner, the claims differ from Trost by using an analogous starting material which differs in having a methyl group at the 4-position of the compound of formula III, and Trost only discloses an unsubstituted 4-position, the starting materials are analogous in that they are both enynes of formula III.

In conclusion, the Examiner states that one skilled in the art would have been motivated to use the process of Trost in order to obtain the instant derivatives since the starting materials would be expected to react similarly.

In response to the Examiner's comment that preparation of the 20S form would have been obvious when Miyamoto discloses 20R forms, Applicants submit that where a method for preparing a purified isomer of a compound such as the 20S form is not taught or suggested by the cited reference, then a *prima facia* case of obviousness has not been established. Applicants rely on the decision from Emory University v. Glaxo Wellcome, Inc. (44 USPQ2d 1407 (DC NGa 1997)) citing In re Hoeksema (158 USPQ 596, (CCPA 1968)) for the holding that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public".

In addition, the compound of Claim 2 is an intermediate compound rather than a starting material as incorrectly stated by the Examiner, and the intermediate compound is essential for

the claimed process with respect to the preparation of any of the seven diastereomers claimed in Claim 1.

Applicants submit that the Examiner has not established a prima facia case of obviousness and that the rejection of Claim 2 is improper. Accordingly, reconsideration and withdrawal of the rejection is requested.

III. Response to objection to the data in the specification

The data on page 39 of the specification are objected to for not demonstrating the unexpected results for the invention.

According to the Examiner, the comparative experiments do not demonstrate unexpected results obtained with the instant 20S compound compared to 20R, and therefore an explanation or more technical comparative data are required to meet this objection.

Applicants submit that the comparative data in Example 9 of the specification and the Declaration evidence enclosed herewith, demonstrates, unequivocally, the unexpected results obtained with the instant 20S compounds compared to the 20R forms, and that the Examiner's objection is met.

IV. Response to objection to Claims 1 and 2

The Examiner states that by bracketing the phrases in each of Claims 1 and 2, Applicants are suggesting that the subject matter should be deleted. Accordingly, to correct this error, the brackets should be deleted.

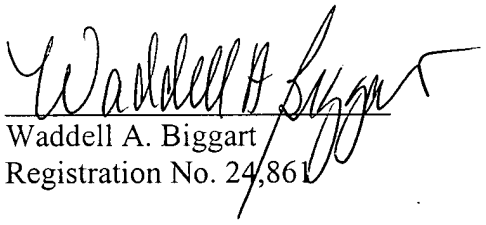
The deletion of the brackets from Claims 1 and 2 responds to this point, and accordingly renders the Examiner's objection moot.

CONCLUSION

In view of the foregoing, reconsideration and allowance of this application are now believed to be in order, and such action is hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned at the telephone number listed below.

Applicants hereby petition for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,



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